Evaluation of the use and handling of three different pen systems considered for in vitro fertilization treatment

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Abstract: OBJECTIVE The objective of this study was to assess and compare the features of the Bemfola, Gonal-f and Puregon injection pens. METHODS Females who intended to undergo hormonal treatment received the three different pens in a randomized, consecutive sequence. For each of the pens, the potential patients completed an Injection Pen Assessment Questionnaire, as well as a questionnaire comparing the handling, convenience and preference among the three pens. RESULTS The mean score on the visual analogue scale (VAS) for the Bemfola pen (BP) was 77.8 ± 14.0; for the Puregon pen (PP), 72.1 ± 12.4; and for the Gonal-f pen (GP), 68.6 ± 16.4. The BP was superior to both competitor devices in pen size, inconspicuousness, ease of use and dose changing; no significant differences to both competitor pens were observed in the way the pen looks, the way the pen feels and the ease of injection of the volume. The 'overall' assessment was significantly better for the BP when compared to the GP ($p = 0.0019$), while no significant difference was observed between the BP and the PP. CONCLUSIONS This study demonstrated significantly higher ratings for pen size, inconspicuousness, ease of use and dose adjustment for the BP compared to other marketed pens.

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Abstract

Objective: The objective of this study was to assess and compare the features of the bemfola vs. Gonal-f and Puregon injection pens.

Methods: Females who intended to undergo hormonal treatment received the three different pens in a randomised, consecutive sequence. For each of the pens, the potential patients completed an Injection Pen Assessment Questionnaire (IPAQ), as well as a questionnaire comparing the handling, convenience and preference among the 3 pens.

Results: The mean score on the visual analogue scale (VAS) for the bemfola pen was 77.8±14.0, followed by the Puregon pen (72.1±12.4) and the Gonal-f pen (68.6±16.4). The bemfola pen was superior to both competitor devices in pen size, inconspicuousness, ease of use, and dose changing; no significant differences to both competitor pens were observed in the way the pen looks, the way the pen feels, and the easiness to inject the volume. The "overall" assessment was significantly better for the bemfola pen when compared to the Gonal-f pen (p=0.0019), while no significant difference was observed between the bemfola and Puregon pens.

Conclusions: This study demonstrated significantly higher ratings for pen size, inconspicuousness, ease of use and dose adjustment for the bemfola pen compared to other marketed pens.

Keywords: Appearance and perception of bemfola pen, preference and convenience of bemfola pen, overall ranking pen systems

Introduction

Follicle stimulating hormone (FSH) is a pituitary glycoprotein hormone that plays a key role in regulating reproductive function in both males and females. Recombinant human FSH (r-hFSH), such as Gonal-f and Puregon, have been in widespead use since the 1990s[1]**.** Biosimilar versions of r-FSH have recently been developed in order to provide economically attractive r-hFSH alternatives of high quality.

Bemfola, a biosimilar-r-hFSH, is delivered in a novel, innovative injector pen system (reddot design award 2011). The bemfola pen is a single-use, disposable pen available in 5 different dose strengths (i.e., 75IU, 150IU, 225IU, 300IU and 450IU). The bemfola pen allow a fine-tuned dosing adjustment in 12.5IU and 25IU increments. Other characteristics of the single-use pen are volume and injection-control mechanisms by visual aids such as coloured bars indicating the injection volume. The clearly legible selected dose (as well as a click signal after successful copmletion of the injection) avoid dosing errors, which in turn may improve therapy compliance. If patients need a lower dose than the maximum ejection volume, an in-built lock prevents re-use of the pen device in order to reduce redosing for patient safety. The remaining dose is discarded.

Non-compliance to hormonal treatment regimens represents a critical obstacle to reaching therapeutic goals[1-4]. The use of pens by patients is often limited by factors such as fear of injection, but correct use of the pen can be also related to the device itself. Accordingly, easy-to-use devices may positively influence patient compliance.

The convenient and simple handling of a pen would be expected to increase adherence to the prescribed treatment regimen and therefore lead to a higher success rate of hormonal treatment.

The objective of this study was to assess and compare the features of the bemfola vs. Gonal-f and Puregon injection pens.

Material and Methods

This investigation was conducted as a non-invasive survey and thus did not require ethics approval. Two fertility centres, one each in Switzerland and the United Kingdom, participated in this investigation.

Study Population: The investigation was conducted in female subjects who considered undergoing hormonal treatment for the first time. None of the study subjects had ever previously used any pen medication delivery system. A total of 65 female subjects between 25 and 40 years of age participated in this study.

Materials: The materials used were the bemfola pen (described in this section as BP; Finox AG, Switzerland), Gonal-f pen (described in this section as GP; Merck Serono AG, Switzerland and United Kingdom, and Puregon pen (described in this section as PP; MSD Merck Sharp & Dohme AG, Switzerland). Each pen was provided as a part of a training kit containing saline solution or water for injection but otherwise identical to the commercial version.

Study Design: Female patients who intended to undergo hormonal treatment received the 3 pens in a randomised, consecutive sequence. Subjects completed an

Injection Pen Assessment Questionnaire (IPAQ)[6-7] and thereafter completed a concluding questionnaire comparing the handling, convenience and preference among the 3 pens. All data were collected anonymously. Six alternative sequences of pens (BP-GP-PP / BP-PP-GP / GP-BP-PP / GP-PP-BP / PP-GP-BP / PP-BP-GP) were possible and randomised according to a randomisation list. Consecutive User IDs (01 to 36) indicated for each user a randomly assigned sequence. Users received the 3 pens one after the other in a randomly indicated sequence.

Testing Procedure: Subjects were informed about this survey by the treating physician or study nurse during regular visits at the fertility centre while discussing an anticipated hormonal fertility treatment. Upon receiving the subject's consent to participate, the treating physician or the study nurse conducted the survey. Each subject was instructed by the treating physician or the study nurse and tested consecutively all 3 pens (cross-over design with random sequence). The treating physician or the nurse explained how to use the first of the 3 pens (BP, GP or PP); subjects were instructed to start with an intended administration of 225IU a day followed by a dose increase to 300IU. The instruction included also the use of the closing cap as well as disposing of the needle after injection. The subject then independently completed the entire handling procedure (without help or support from the study nurse or the treating physician) with the first pen. The pen contents were injected into a demonstration cushion. Afterwards the subject's responses were recorded in the first questionnaire (Q1). This procedure was repeated exactly the same way for the second and for the third pen, then completing the second questionnaire (Q2) and the third questionnaire (Q3) respectively. After the

evaluation of all 3 pens was finished, subjects were asked to complete a concluding questionnaire (QEnd), comparing the handling, convenience and preference of all the 3 pens.

Assessments: Information on baseline characteristics (i.e., age and confirmation that potential patients had never previously used a pen delivery system for IVF treatment) was collected from each subject. Questionnaire structure for each pen (Q1, Q2, Q3) addressed appearance and perception (size, handling during injection, overall opinion) as well as comparative preferences and convenience at the end (QEnd). The following scores were used: 1=best pen, 2= second best pen, 3=last choice).

Statistical methods: Complete Case Record Forms (CRFs) consisting of Q1, Q2, Q3, and QEnd were collected; single data entry was made on an Oracle database and descriptive statistics were performed. The pre-defined objective for reported features of pens defined a difference of 20±50 on the VAS score (0 to 100) as significant when BP was compared with GP and PP, respectively. A sample size of 52 had an 80% power to detect a difference in means of 20 (e.g., a first-condition mean [μ_1] of 50 and a second-condition mean [μ_2] of 30) assuming a standard deviation of differences of 50 and using a paired t-test with a 0.050 2-sided significance level. In order to compensate for potential drop-outs and invalid completion of CRFs, a population of 60 users was considered to be sufficient. All users who completed questionnaires for all 3 pens and the final assessments (Q1, Q2, Q3 and QEnd) were included in the analysis. User-reported outcomes (VAS Scores) and ranking scores were assessed using descriptive statistics. The T-test for quantitative data was used

117 to analyse all VAS scores of all items for the 3 pens, while the preference ranking
118 score was assessed with a Wilcoxon signed-rank test for categorical data.
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Results

The highest numerical mean VAS scores were observed for the bemfola pen in 10 out of 11 items-(table 1 and figure 1). As a consequence, the overall mean score of the bemfola pen was the highest with 77.8±14.0 followed by the Puregon pen (72.1±12.4) and the Gonal-f pen (68.6±16.4).

Statistical analysis revealed significantly higher VAS scores for the bemfola pen in 8 out of 11 items when compared to the Gonal-f pen, and in 4 out of 11 items when compared to the Puregon pen. The bemfola pen was superior to both competitor devices in pen size, inconspicuousness, ease of use, and dose changing; no significant differences to either competitor pen were observed in the way the pen looks, the way the pen feels, and the easiness to inject the pen volume (table 1). The "Overall" assessment was significantly better for the bemfola pen when compared to the Gonal-f pen ($p=0.0019$), while no significant difference was observed between the bemfola and Puregon pen.

The bemfola pen showed the highest proportion of "best" choice in all 8 preference and convenience items (table 2 and figure 2). The total mean proportion of the "best" ranking for the bemfola pen was 62% and markedly higher compared to the mean proportion for the "best" ranking for the Puregon pen (26%) and the Gonal-f pen (12%). The proportion of "last" ranking was highest in 5 items (size, appearance, holding, inconspicuousness, and injection performance) for the Gonal-f pen and in 2 items for the Puregon pen (learning of use and injection preparation) and similar for

both pens, the Gonal-f pen and the Puregon pen, with regards to injection handling (handling after the injection).

Statistical analysis revealed significantly better rankings for the bemfola pen in 7 out of 8 items when compared to the Gonal-f pen, and in 4 out of 8 items when compared to the Puregon pen (table 3). The bemfola pen showed a superior ranking to both comparator pens for 4 items (pen size, learning of use, injection preparation, and injection handling), while no significant difference to either comparator pen was observed for one item (injection performance).

Discussion

This study conducted in Swiss and British fertility centres included 65 female subjects considering a therapy with FSH. In addition, this non-invasive study aimed to analyse the appearance, perception and handling as well as the convenience and preference of the bemfola pen and to compare these features and preferences with the widely used Gonal-f and the Puregon pens. Results demonstrated significant benefits and preferences for the bemfola pen compared to the Gonal-f and the Puregon pen. Highest mean VAS scores in 10 of 11 features were observed for the bemfola pen, which also had the highest proportion of "best" choice in all 8 items assessing preference and convenience.

Outcomes on features and preferences of the 3 pens were consistent for the majority of assessments. The bemfola pen showed higher VAS scores and clearly better rankings for the pen size, the learning and facility in using the pen compared to both Gonal-f and Puregon pens. The "inconspicuousness" of the bemfola pen was a significantly better feature compared to both competitors and showed a significantly higher preference when matched to the Gonal-f pen, while the preference compared to the Puregon pen showed a positive trend in favour of the bemfola® pen ($p=0.0615$).

The VAS scores of the bemfola pen on the appearance ("how the pen looks") and feel ("how the pen feels") were similar when related to both challengers, while the preference of the bemfola pen on appearance ("how the pen looks") and handling ("holding in your hands") was significantly higher when compared to the Gonal-f

pen. There were also features such as injecting the volume or the preference on performing the injection which were comparable for all three pens, while the preference for handling after the injection was rated significantly higher for the bemfola pen compared to both the Gonal-f and Puregon pens.

The results showed also clearly that the bemfola pen was superior to the Gonal-f pen with regards to the features on priming and overall use of the pen as well as the setting and changing the doses. This is reflected by the significantly higher preference for preparing the injection, while the ratings of these features were similar between both bemfola and Puregon pens.

In conclusion, the results of this study demonstrated the benefits of the bemfola pen, as well as the potential patients' preference for the bemfola pen compared to available alternatives. These differences were considerable when compared to the Puregon pen and even more marked regarding the Gonal-f pen based on the potential patients' assessments. These findings suggest that the ease, look and handling of the bemfola pen may potentially translate to increased patient preference and compliance which requires additional study.

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Declaration of Interest

The study was funded by Finox AG, Switzerland. The authors B. Imthurn, R. Stiller and M. Arnold are employees of the University Hospital of Zürich. The authors E. McVeigh and F. Pringle are employees of the Oxford Fertility Centre. The authors Ch. Irps and M. Rettenbacher are employees of Finox AG. Besides Ch. Irps and M. Rettenbacher, there is no financial relationship with the authors.

	bemfola		Gonal-f		Puregon		bemfola vs. Gonal-f	bemfola vs. Puregon
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-value**	**p-value**
Appearance and perception								
Size of the pen	77.5	±18.8	62.2	±22.4	65.5	±22.0	<0.0001	0.0016
The way the pen look	65.0	±23.0	59.6	±23.5	65.7	±22.5	n.s.	n.s.
The way the pen feels	71.8	±20.4	65.4	±22.5	67.5	±17.7	n.s.	n.s.
The inconspicuousness of the pen	72.0	±20.5	57.5	±25.1	60.5	±22.2	0.0006	0.0035
How easy was it to learn how to use the pen	84.9	±14.2	74.1	±17.4	76.0	±17.0	<0.0001	0.0009
Handling of pen during injection								
Priming the pen	81.8	±16.5	74.8	±16.2	76.6	±16.0	0.0004	n.s.
Setting the dose	83.8	±18.4	77.1	±19.6	80.9	±15.0	0.0238	n.s.
Changing the dose	86.9	±13.3	71.9	±20.4	75.3	±20.3	< 0.0001	< 0.0001
Injecting the volume	74.1	±23.4	71.4	±24.9	72.6	±21.9	n.s.	n.s.
Knowing when the injection pen has been completed	78.6	±21.8	68.5	±25.9	78.1	±15.6	0.0017	n.s.
Overall								
How easy was it overall to use the pen	79.7	±18.2	72.4	±18.1	74.8	±17.0	0.0019	n.s.
Total mean of scores	**77.8**	±14.0	**68.6**	±16.4	**72.1**	±12.4		

Table 1: Mean (±SD) VAS Scores (0 to 100) and p-values of 11 items assessing the appearance, perception and handling of the bemfola, Gonal-f and the Puregon pens

232

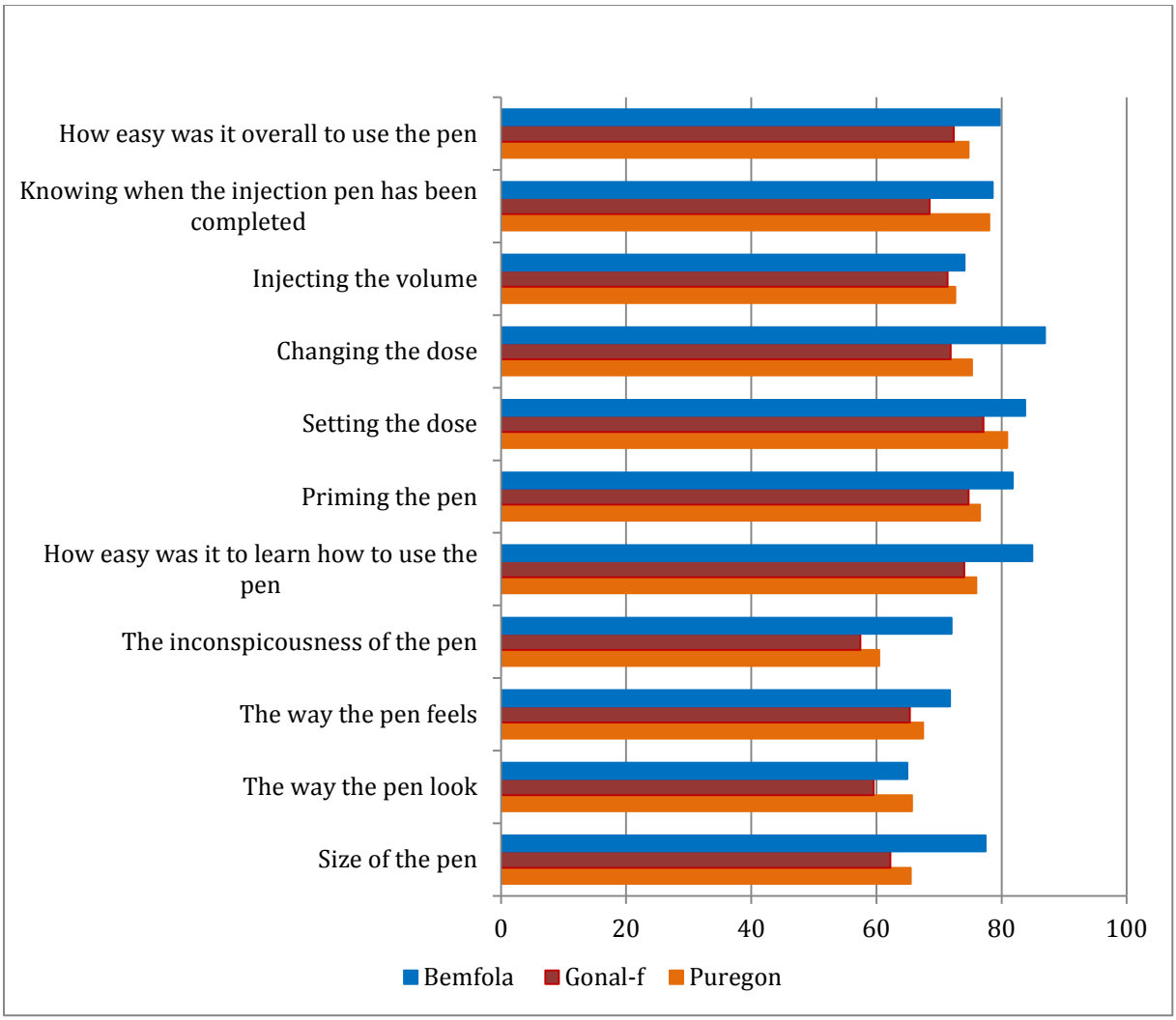

Figure 1: Mean VAS Scores (0 to 100) of 11 items assessing the appearance, perception and handling of the bemfola, Gonal-f and the Puregon pens

Preference and convenience	bemfola			Gonal-f			Puregon		
	Best	**Second**	**Last**	**Best**	**Second**	**Last**	**Best**	**Second**	**Last**
Size of the pen	**75%**	8%	17%	3%	51%	46%	22%	43%	35%
The way the pen look like	**46%**	26%	28%	15%	46%	38%	38%	29%	32%
Hold the pen in your hands	**55%**	15%	29%	11%	49%	40%	34%	37%	29%
Inconspicuousness of the pen	**65%**	12%	23%	3%	55%	42%	32%	34%	34%
Learning how to use the pen	**69%**	12%	18%	11%	54%	35%	18%	37%	45%
Preparing the injection	**74%**	11%	15%	8%	60%	32%	17%	34%	49%
Performing the injection	**37%**	25%	38%	31%	38%	31%	34%	38%	28%
Handling after the injection	**71%**	14%	15%	12%	45%	43%	15%	42%	43%
Total mean of ranking	**62%**	15%	23%	**12%**	50%	38%	**26%**	37%	37%

Table 2: Ranking (percent of best, second and last ranking) of 8 items assessing the preference and convenience of the bemfola, Gonal-f and the Puregon pens

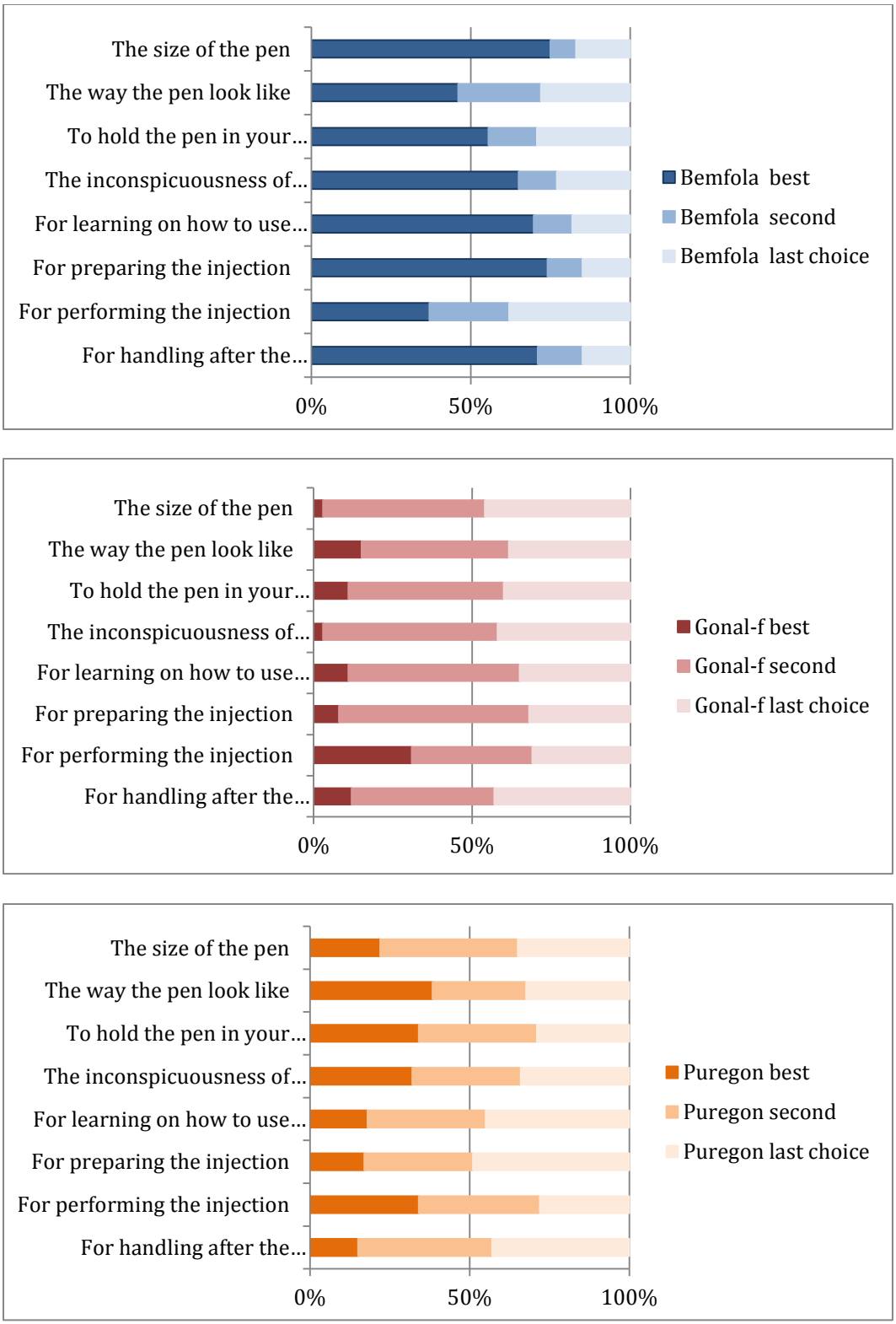

Figure 2: Ranking (percent of best, second and last choice) of 8 items assessing the preference and convenience of the bemfola, Gonal-f and the Puregon pens

Preference and convenience	bemfola vs Gonal-f	bemfola vs Puregon
	p values	p values
The size of the pen	< 0.0001	0.0004
The way the pen look like	0.0183	n.s.
To hold the pen in your hands	0.0010	n.s.
The inconspicuousness of the pen	< 0.0001	n.s.
For learning on how to use the pen	< 0.0001	< 0.0001
For preparing the injection	< 0.0001	< 0.0001
For performing the injection	n.s.	n.s.
For handling after the injection	< 0.0001	< 0.0001

246

Table 3: Ranking (percent of best, second and last ranking) of 8 items assessing the preference and convenience of the bemfola, Gonal-f and the Puregon pens

247

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